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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/768,350	01/30/2004	Wei He	170.002	6382

7590 10/20/2004

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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/768,350	HE ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/11/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

This Application was filed January 30, 2004. No priority was claimed.

Claims 1-11 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

According to the MPEP:

> Every patent must contain a written description of the invention sufficient to enable a person skilled in the art to which the invention pertains to make and use the invention. Where the invention involves a biological material and words alone cannot sufficiently describe how to make and use the invention in a reproducible manner, access to the biological material may be necessary for the satisfaction of the statutory requirements for patentability under 35 U.S.C. 112.

The Application describes the isolation of several lines of ES cells obtained from C57 mice. While the method used to establish ES cell lines is well known in the art, and on a macroscopic level, the obtained cells described by the Applicants fit the criteria of an ES cell, each established line can be unique depending on the genetic make up of the mice from which the ES cell was obtained and/or the process in the way the cell was

generated. Because there is no way to ensure that two independent laboratories would necessarily generate the exact same ES cells, down to their most minute detail, it is required that the cell lines described in the specification and in the claims are deposited. For rules of deposit, see CFR 37 1.801-1.809.

Claims 3-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mouse, does not reasonably provide enablement for any non-human vertebrate animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 4 is to a method of producing a genetically modified non-human animal. Claim 4 then lists that the method involves ES cells. However, not all non-human transgenic vertebrate animals can be made via ES cells. These animals include frogs and birds. In the case of frog (*Xenopus*), transgene integration involves an enzyme-mediated step. Sperm DNA is digested briefly with restriction enzyme before the transgene (cut with the same restriction enzyme) is introduced. The sperm extract is then injected into unfertilized eggs (Kroll and Amaya, 1996, Development, 122:3173-3183; page 3174, second column, 8th paragraph, line1 to page 3175, first column, second paragraph, line 5; page 3175, first column, 4th paragraph, lines 15-19). In the case of bird (chicken), to obtain a one-cell egg, a mature hen must be killed, and thus, this makes it difficult to obtain a sufficient number of eggs to successfully complete any procedures for obtaining transgenic birds (Mozdziak and Petitte (2004, Developmental

Dynamics, 229: 414-421; page 415, second column, first paragraph, lines 8-14)). Thus, claim 4 is read only on transgenic animals that can be made via ES cells.

It should be kept in mind that the previous paragraph points out how to generate non-mammalian transgenic animals. However, the art also shows that the only transgenic mammalian animals that can be generated by using ES cells are mouse, pig, and rabbit. According to Murray, et al. (1999, *Transgenic Animals in Agriculture*, CAB International: Oxon, pages 58-61), the "isolation of ES cells has not been accomplished unequivocally in other species, including in domestic livestock (page 59, lines 3-4)." It is possible that putative ES cells have been isolated in other animals aside from the mouse. These include sheep, hamster, pig, cattle, mink, rabbit, rat, monkey and goat. However, in many cases the data characterizing them do not provide the most convincing data (page 59, lines 10-17). Part of the discrepancy stemmed from the fact that scientists were relying on morphological comparisons of mouse ES cells to define what other animals' ES cells should look like. Some scientists added a second level of stringency, identifying ES cells by the fact that they differentiate *in vitro*. However, the best level of stringency that identifies an ES cells is that the cells can differentiate *in vivo* (page 60, second paragraph). In the case where chimeric offspring have been obtained after injection of putative ES cells into blastocysts, the species include mouse, pig, and rabbit (page 59, lines 18-22). Thus, while the art teaches that making transgenic animals via ES cells is limited to these animals, it should be pointed out that the Applicants have taught that they were able to generate transgenic mice from certain mouse ES cell lines that they have generated. The scope of enablement for generating

transgenic mice is limited to these specific mouse cell lines. The reason for this limitation is because there is no guarantee that all ES cells are exactly the same and will necessarily generate the exact same mosaic mouse.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is incomplete. In its present state, claim 3 reads as though one could take a pair of wild type animals, breed them, and obtain genetically modified progeny. On one hand, all progeny are a genetic mixture of their parents. In a broad sense of the term "genetically modified," the term could encompass the blending of genetic information from both parents. On the other hand, claim 3 could be interpreted to mean that a pair of wild type animals could breed and produce progeny with genetic mutations. While occasionally progeny can have genetic mutations, neither the specification nor the art demonstrates specific ways to routinely obtain specific genetic mutations from mere breeding of parental animals.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Tarrant et al. (2002, Molecular and Cellular Biology, 22: 5006-5018). Claims 1 and 2 are broad that they encompass any non-human vertebrate animal cell line. Tarrant et al. teach that mouse W9.5 ES cells derived from a 129/Sv.C3-+^{c}+^{p} inbred strain were electroporated with gene trap vector pMS-1. ES cells were selected for the vector using G418 and each positive clone was differentiated and examined for gene trap vector expression in hematopoietic cells (page 5007, first column, fifth paragraph, Derivation of the gene trap ES cell line 26F8). One particular ES clone was selected for its specific expression in hematopoeitic cells and injected into BALB/c blastocysts to generate transgenic mice (page 5007, second paragraph, lines 1-3).

Claim 3 is rejected under 35 U.S.C. 102(b) as being anticipated by Schuster-Gossler, et al. (2001, BioTechniques, 31: 1022-1026). Schuster-Gossler et al. anticipate claim 3 because they demonstrate that mosaic male mice (of the C57BL/6J line) are bred to coisogenic female mice (of the C57BL/6J-Tyr^{c-2J} line) and generate progeny. The progeny are "genetically modified" from their parents because their genetic information is comprised of genetic information from the mother and father mouse.

Claims 4 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Clouthier et al. (1998, Development, 125: 813-824). Claims 4-5 are to a method of

making transgenic mice via ES cells. This method is well known in the art. Clouthier et al. teach in the Material and Methods section that they designed a mouse with a disruption in the ET_A gene (see section, Gene targeting). The homologous recombination construct, which replaced exons 5 and 6 of the ET_A gene with neo-TK, was electroporated into ES cells (page 84, second column, second paragraph, lines 3-12). Following selection of ES cells that were survived the drug selection with G418 and FIAU, surviving ES cells were further screened by Southern blot to confirm homologous recombination (page 84, second column, second paragraph, lines 13-15). ES cells were injected in blastocysts and allowed to develop. The resultant chimeric mice were tested for germline transmission of the targeted allele (page 84, second column, second paragraph, lines 17-20). The mice selected for germline transmission were then established on an inbred background and were further genotyped by polymerase chain reaction (PCR) on genomic DNA (page 84, second column, second paragraph, lines 20-24).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schuster-Gossler, et al. (2001, BioTechniques, 31: 1022-1026) in view of Wei (1997, Annu. Rev. Pharmacol. Toxicol., 37: 119-41).

Schuster-Gossler, et al. teach that while gene-targeted mice by means of homologous recombination are a valuable tool, the efficient production of them have not always been met. One reason for this inefficiency results from finding the best host blastocyst/ES cell line combination that yields chimeric animals with germline transmission. To generate a transgenic animal, one would carry out the genetic manipulation in the ES cell, introduce the ES cell into a host blastocyst and allow the embyro to develop into a chimeric animal. One way of discriminating whether a cell originated from an ES cell or the blastocyst host is via a genetic marker of the cell, e.g. coat color. Because some ES/transgenic cells may have become germline cells, one would breed the chimeric animal and select the mice that have been derived from the ES cells. Schuster-Gossler, et al. isolated ES cells from C57BL/6J (B6) mice (page 1022, second column, "B6 ES Cell Derivation and Culture," lines 1-8). B6 ES cells that had gone through 9-17 passages were thawed from liquid nitrogen and then injected into blastocyts from a coisogenic mouse, c^{2J}, or a noncoisogenic mouse, FVB (page 1022, third column, "Generation of Chimeric Mice," lines 1-9. Coat color was used to determine whether the cells had come from the ES cell (black) or from the blastocyst (white). The male mosaic mice were then mated to c^{2J} female mice to determine the germline transmission (page 1023, third column, first paragraph, lines 7-11). The ability of the host blastocyst to colonize ES cells was determined. It was found that when the

B6 ES cells were injected into the coisogenic blastocyst, more mice had a higher degree of chimerism that had been contributed by the ES cell (i.e., more of their body was black). When the chimeric mice were bred, all but one mouse that were made with B6 ES cell/c^{2J} blastocyst (coisogenic), i.e. the same genetic background had had ES-derived offspring (black). However, only 2 of 14 mice made from B6 ES/FVB blastocyst (non-coisogenic) produced ES cell-derived mice (page 1025, second column, lines 17-21). Furthermore, coisogenic mice were transmitting the ES lineage more frequently than the non-coisogenic mice (page 1025, second column, line 22 to third column, line 7). While Schuster-Gossler et al. teach that other strains of mice can be used to generate transgenic mice and that using host blastocysts that are coisogenic with the ES cell produces more viable ES cell-derived mice. However, Schuster-Gossler et al. do not teach how to make transgenic mice.

Wei teaches that microinjection of purified DNA into the pronuclei of fertilized, one-cell eggs were one method for introducing DNA molecules (page 120, second paragraph, lines 9-12). While the creation of mice by pronuclear injection was efficient and consistent, some problems associated with it included an inability to control sites of integration and copy number of transgenes. Sometimes, the genes that were integrated were toxic. Random integration and multiple copies of transgenes sometimes lead to unregulated expression of transgenes and caused side effects (page 120, third paragraph, lines 3-8). To circumvent these issues, a technique that can deliver a single copy of a mutated gene to a specific target site was developed (page 120, third paragraph, lines 7-8).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use mice with a different genetic background than the ones commonly used in transgenic studies (129-derived line), given the results of Schuster-Gossler et al. teaching that the ES cell and host blastocyst need to be coisogenic to produce viable offpring that transmit the ES cell genotype at a high rate. Transgenesis, as taught by Wei, is a frequent way to introduce changes in the mouse genome. There would have been a reasonable expectation of success given the results of Schuster-Gossler et al. teaching how to produce viable offspring that transmit the ES cell genotype at a high rate in a different strain of mouse, and the result of Wei teaching methods of generating transgenic mice.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is (571) 272-2911. The examiner can normally be reached on Monday-Friday 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, Ph.D. can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JH

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